Research Square

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Molecular Dynamics Study of Polyphenolic and Flavonoids of Momordica charantia with Glucagon-Like Peptide-1 (GLP-1) of Dipeptidyl Peptidase-4 (DPP4)

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Abstract

Diabetes mellitus is a serious global health concern. In this research, flavonoids and polyphenolic compounds from the *Momordica charantia* were searched for the potential inhibitor against dipeptidyl peptidase IV inhibitor through the *in-silico* techniques.

First, we screened out selected compounds based on molecular docking binding score and those with good binding affinity are selected for the further molecular dynamics study and Absorption, Distribution, metabolism, Extraction (ADME). Molecular docking study revealed four phytoconstituents as potential compounds such as quercetin, catechin, naringenin and epicatechin. Further, RMSD and RMSF study shows quercetin has stable configuration than catechin. Drug likeness profile shows all selected candidate follow the Lipinski's rule and Vaber rule.

Based on computation study from the *Momordica charantia* plant quercetin and catechin are the highly potential compound. These compounds have the highest molecular docking score, good drug-likeness profile and stable RMSD and RMSF plot.

1. Introduction

Diabetes mellitus is a serious global health concern. In developed countries, type 2 diabetes accounts for more than 90% of cases [1-4]. It is estimated that 10% of people in the USA suffer from diabetes. One of the main areas of research for the creation of novel medications to treat type 2 diabetes is the identification of small-molecule inhibitors of the enzyme dipeptidyl peptidase-IV (DPP-IV) [5-8]. A serine protease called DPP-IV cleaves dipeptides from peptide substrates containing proline (or alanine) in the penultimate position. It belongs to the prolyl oligopeptidase family [9, 10]. The incretin hormones glucose-dependent insulinotropic peptide (GIP) and glucagon-like peptide-1(GLP-1) are inactivated by DPP-IV [11, 12]. Following a meal, these hormones play a crucial role in the release and utilization of insulin. Nowadays, GLP-1-based therapy is a very effective way to treat type 2 diabetes [13]. When administered intravenously, GLP-1 exhibits remarkable efficacy in humans, reducing blood glucose levels and modulating insulin levels in a glucose-dependent manner, all while lowering the risk of hypoglycemia. By blocking DPP-IV, the fast ($t_{1/2}$ < 1 min) degradation of GLP-1 is inhibited, which raises the hormone's circulating levels *in vivo* and extends its advantageous effects [1, 14, 15].

A class of antihyperglycemic drugs known as dipeptidyl peptidase 4 (DPP-4) inhibitors is used to treat type 2 diabetes mellitus, a major risk factor for heart failure, stroke, coronary disease, and many other cardiovascular diseases [8, 16]. This activity goes over the different medications in this class, as well as the indications, side effects, activity, and other important aspects of DPP-4 inhibitor therapy in a clinical setting. It also goes into further detail about the fundamental knowledge that every member of an interprofessional team overseeing the treatment of patients with diabetes needs.

Dipeptidyl-peptidase (DPP) 4, commonly referred to as CD26, is a 110 kDa glycoprotein that is widely expressed and was initially described by Hopsu-Havu and Glenner. Shedding is the process by which

DPP4, a type II transmembrane protein, cleaves off the membrane and enters the bloodstream(Mannucci et al., 2005). Since the approval of DPP4 inhibitors for the treatment of type 2 diabetes mellitus (T2DM), the significance of DPP4 for the scientific and medical community has increased significantly [17]. The post-prandial insulin action is prolonged by these so-called gliptins because they raise incretin levels. Soluble DPP4 may also be a significant molecular biomarker because it is classified as an adipokine and correlates with metabolic syndrome parameters [18]. The multifunctional enzyme DPP4 binds to many different peptides, including extracellular matrix proteins and adenosine deaminase (ADA) [9]. Furthermore, DPP4's complexity of action is increased by the fact that it is a serine protease that cleaves a wide variety of substrates. DPP4 is therefore implicated in immune cell activation and signaling pathways. Its dysregulated expression and release are linked to a variety of illnesses [19-21].

Many cultures have long utilised *Momordica charantia*, also referred to as bitter melon or bitter gourd, as a treatment for diabetes [22, 23]. Research indicates that bitter melon may be beneficial for diabetics, and numerous studies have examined its possible effects on insulin sensitivity and blood sugar levels [24, 25]. Here are some important details about how it might be used to treat diabetes. Several bioactive substances found in bitter melon, such as vicine, polypeptide-p, and charantin, are thought to have hypoglycemic (blood sugar-lowering) properties [26, 27]. These substances may enhance the release of insulin, the absorption of glucose by cells, and the metabolism of glucose, all of which contribute to blood sugar regulation. Bitter melon may improve insulin sensitivity, which is important for people with type 2 diabetes, according to certain studies [27-29].

In this research, we are searching for the potential inhibitor against dipeptidyl peptidase IV inhibitor through the *in-silico* techniques such as molecular docking, drug likeness properties and molecular dynamics study. For this study, we have selected flavonoids and polyphenolic compounds from the *Momordica charantia* based on previous publications.

2. Material and Methods

2.1 Selection and preparation of ligand: *Momordica charantia* has been known for its anti-diabetic activity from ancient times in folk fore medicine. Therefore, in our study, we selected some of the phytoconstituents from the plant based on previous literature [28, 30]. In various literature, it was mentioned that secondary metabolites such as flavonoids and polyphenolic compounds have shown significant activity in diabetes. In Table 1 we have presented various selected ligands, structure of the molecules and pubchem ID. The structure of all the phytoconstituents was drawn using ChemDraw Ultra 6.0 (Chem office package) with accuracy in aromaticity and energy minimization of the structure was performed using chem3D Ultra 6.0 (Chem office package). After that, we added kollaman charges on the ligand and converted the structure into .pdbqt format using Autodock 1.5.6.

2.2 Protein preparation: The crystal structure of porcine dipeptidyl peptidase IV (Cd26) in complex with a low molecular weight inhibitor (PDB ID: 2BUA) was retrieved from the protein data bank (PDB). The crystal structure of the protein was cleaned up using Discovery Studio 2022 Client (BIOVIA) by removing

water molecules, hetero-atoms and ligands molecules. After clean-up structure, we added polar hydrogen bonds because polar hydrogen can be involved in the bond formation with the ligand and that might be the important scenario to look after in the docking study while non-polar hydrogens are not necessary to add. Further, Gasteringer charges were added into protein structure and missing amino acids residues were repaired using Autodock 1.5.6. Version.

2.3 Molecular docking: After preparing ligands and protein ready for the molecular docking, we set up the grid box to dock the ligand in the active site of the amino acids. The grid box of the DPP-4 protein was set up (60⁎60⁎60) in all the axis of the active site of the amino acids. After setting all the ligands were docked on the predefined grid box individually [31]. The docking complex was again converted into protein data bank (pbd) file for easy visualization in Discover Studio 2020 Client. In discovery studio, we generated the two-dimensional (2D) and three dimensional (3D) interactions of all the molecules with DPP-4 protein [32, 33].

2.4 Drug Likeness properties: To consider any small molecules as a drug, we must consider serval physiochemical and pharmacokinetic properties of the molecules. The proper prediction of the molecules physiochemical and pharmacokinetic properties can save huge amount of time and money for the researcher and industry. Therefore, researcher use several *in-silico* tools among them most trusted one is Swiss Absorption, Distribution, metabolism, Extraction (ADME) predictor [34].

2.5 Molecular dynamic study: The molecular simulation study was performed for the lowest binding molecule from molecular docking study. Protein inside the body is dynamics and it changes with time interval and impact on the ligand protein interaction. Therefore, we first temperature coupling and pressure coupling of the system. Afterwards, we have to minimize the energy of the system to perform the molecular dynamics steps up to 300 ns. Molecular simulation will help to understand the stability of the bonding of the ligand with the amino acids throughout the 300 ns. The Gromacs 2022 version was used to measure the fluctuation of the different parameters [35].

2.6 Analysis of molecular dynamics: In this study, we perform the root mean square deviation (RMSD) of the amino acids and root mean square fluctuation of the particular set of the amino acids. This will help us to predict the stability of the ligand in the protein surface for some time interval. For this study, we performed the RMSD 300 ns time interval and RMS fluctuations of the highly fluctuating molecule. To validate the result of the study, we performed the triplicate, keeping all the parameters identical.

2.7 Statistical analysis: The data presented in the paper are reviewed using different software such as Discovery Studio 2022 client, Auto dock 1.5.6 version and QT Grace. The high-resolution docking images were created using the Discovery Studio 2022 client, three-dimensional protein structure were generated using the Auto dock 1.5.6. Molecular dynamics simulations images were created using QT Grace Software.

3. Results and discussion

3.1 Molecular docking: To understand the ligand-protein structural interaction in three-dimensional and two-dimensional space, we designed the *in-silico* molecular docking study. The molecular docking study of the selected compounds showed good binding affinity. The reason behind the better binding affinity is

because of the formation of the hydrogen bonds between the ligands and the protein. All our selected compounds are flavonoids and polyphenolic compounds having hydroxyl groups that make it prone to the formation of the h-bond. In our study, quercetin has shown strongest binding affinity in comparison to all other ligands with − 6.20 Kcal/mol. Quercetin has five hydroxyl groups, therefore, it can bind properly in the binding pocket of the dipeptidyl peptidase IV protein pocket. Further, catechin, naringenin, and epicatechin have 6.13 Kcal/mol, 6.0 Kcal/mol, and 5.95 Kcal/mol binding energy respectively. Quercetin has interacted with three amino acids sequences of the dipeptidyl peptidase protein in the deep pocket. Among the five hydroxyl groups present in quercetin only two of them form the hydrogen bonds other remaining are forming Vander walls interactions. 3-number of carbons in quercetin formed two hydrogen bonds with ALA 447 and VAL 443, the remaining 4’ carbon formed the hydrogen bond with SER 156. Even though, epicatechin have four number of hydrogen bonds at GLU 503 (2), ALA 446(1), and VAL 443(1), quercetin has lowest binding affinity, which indicates that ALA 447, VAL 443 and SER 156 potential target amino acids residues of our target DPP4 protein. In VAL 443 amino acids are common in both complexes, which makes it more crucial target residues to attack to inhibit the DPP4 protein. Catechin is our second lowest binding energy compound, which forms only one h-bond, which is with VAL 443. Catechin-DPP4 inhibitor further strengthens our discussion on VAL 443. A therapy for type 2 diabetes that lowers glucose levels is dipeptidyl peptidase (DPP)-4 inhibition. Inhibitors of DPP-4 work through the classical mechanism of inhibiting DPP-4 activity in peripheral plasma. This keeps the peripheral circulation's supply of the incretin hormone glucagon-like peptide (GLP)-1 from being inactivated. In this crucial mechanism, VAL 443 amino acid residue has shown a very important role. Table 2 illustrate the binding energy, number of hydrogen bonds and hydrogen bond forming amino acids residue. Further, Fig. 1 shows three dimensional (left) and two dimensional structure (right) of the four lowest binding ligands with GLP-1 protein.

Table 2

The molecular docking study of those selected compounds showed quercetin has the lowest binding energy score, which makes it to bind tightly with the DPP-4 inhibitor. However, epicatechin shows the highest number of the hydrogen bonds. In the docking study, we found out that VAL 443 amino acids shows crucial amino acids for the hydrogen bond formation.

S.N.	Name of Compounds	Docking score (– Kcal/mol)	No. of hydrogen bonds	Amino acids that interact with ligand through H-bond
1	Caffeic acid	4.65	1	ASP 454
2	Catechin	6.13	1	VAL 443
3	Ellagic acid	5.55	1	SER 156
4	Epicatechin	5.95	4	GLU 503, ALA 446 and VAL 443
5	Ferulic acid	5.20	1	SER 156
6	Naringenin	6.0	2	GLU 503 and PHE 504
7	Protocatechuic acid	4.61	1	SER 508
8	Quercetin	6.20	3	ALA 447, VAL 443 and SER 156

3.2 Root mean square deviation: We have selected the quercetin and catechin for the further molecular dynamics study. To validate the data of molecular dynamics, we have performed the triplicate of those two compounds within 300 ns of time interval to observe the root mean square deviation. First of all, quercetin shows relatively stable in all three replica with deviation from 0.1–0.3 nm, however, third replica on green color shows little bit more deviation than the other replica and gone up to 0.35 nm. Secondly, we also performed the molecular dynamics of the catechin using the same conditions with three replica. In this condition, second replica of the catechin shows high deviation from 25 ns to 200 ns. From 0 ns to 25 ns, it has 0.1 nm of deviation after that it suddenly raise to 0.6 nm for 25 ns to 125 ns. Then afterwards, it come down to 0.4 nm till 200 ns and continue as 0.35 ns for remaining 100 ns of MD study. While remaining two replica 1 and replica 3 are stable at 0.1–0.2 nm throughout the MD run. In the Fig. 2, we can see the time vs RMSD distance plot for quercetin and catechin. The result of the RMSD run shows that quercetin form relatively stable complex with all the replica at around 0.1–0.3 nm.

3.3 Root mean square fluctuations: We performed the RMSF fluctuations of the highly fluctuating amino acids of two selected compounds. The quercetin-DPP4 complex shows maximum fluctuations up to 250 amino acids residue while catechin-DPP4 complex shows fluctuation up to 300 amino acids residues. The quercetin complex have several fluctuating amino acids residues than catechin complex. Quercetin-DPP4 complex has maximum number of amino acids fluctuations from starting to 250 amino acids residue. Catechin-DPP4 complex has relatively smaller number of amino acids fluctuations. Figure 3 shows the root mean square fluctuations of the highly fluctuating amino acids residues of quercetin and catechin. Most importantly, starting 0–50 amino acids (starting from 0.47 nm to 0.1 nm) and 250–300

amino acids (start from 0.1 nm and raise upto 0.65nm and again come do 0.1 nm) residues of the catechin-DPP4 complex are relatively not stable which plays the significant role in the finding the relatively stable and unstable amino acids residues.

3.4 Drug-Likeness Properties: In our study, we looked for the physiochemical properties of the top docking score compounds such as quercetin, catechin, naringenin, and epicatechin. We predicted the important physiochemical parameters of the drug that are necessary to design the drug. The number of rotable bonds on the compounds plays crucial role to consider as a drug. If the compound have (less than or equal to 10) rotatable bonds that compound is good for oral bioavailability. Our all selected compounds have only one rotatable bonds therefore, all the selected compounds are good in oral bioavailability. The impact of hydrogen bond donors and acceptors on passive diffusion across cell membranes plays an essential step during drug absorption and distribution. Less than ten hydrogen bond acceptors and no more than five hydrogen bond donors are found in the majority of orally active medications. An oral medication should, in accordance with Lipinski's Rule of 5, have a LogP value < 5, ideally between 1.35 and 1.8 for optimal intestinal and oral absorption. None of our selected molecules were violating Lipinski rule of 5, this suggests that our selected compounds have good physiochemical properties. Further, GI absorption and lead likeness of the selected compounds are good. In terms of synthetic accessibility, all the selected compounds seems like easy to synthesize on the lab as their score are below 3.50 (0 means easy synthesis and 10 means difficult to synthesis). Table 3 describes the overall statistical data of physiochemical properties of lowest binding energy ligands.

Table 3
Illustrate the physiochemical parameters and quercetin, catechin, naringenin and epicatechin. All selected compounds follows the Lipinski's rule of 5 and Veber rule. Those two parameters are significant in terms of absorption, distribution and oral bioavailability. Compounds are feasible for easy synthesis in the lab.

Physiochemical Properties	Quercetin	Catechin	Naringenin	Epicatechin
n-rotb	1	1	1	1
n-HbA	7	6	5	6
n-HbD	5	5	3	5
Ilog P	1.63	1.47	1.75	1.47
Lipinski violations	0	0	0	0
GI absorption	High	High	High	High
Leadlikeness	Yes	Yes	Yes	Yes
Synthetic accessibility	3.23	3.50	3.01	3.50

4. Conclusion

Our *in-silico* study provide molecular interactions of the amino acids of DPP4 protein involved in type 2 diabetes mellitus with various selected ligands from *M. charantia* plants. In the context of glucose metabolism, DPP4 inhibition has become an important therapeutic target for the management of type 2 diabetes mellitus. Inhibiting DPP4 activity prolongs the half-life of GLP-1 and GIP, leading to increased insulin secretion, decreased glucagon release, slowed gastric emptying, and improved glycemic control. Molecular docking study showed that quercetin and catechin have lowest binding energy with DPP4 protein (VAL 443). ADME profile of the all four selected compounds quercetin, catechin, naringenin, and epicatechin follows the Lipinski's rule of 5. Molecular dynamics study of those two selected compounds also shows relatively stable complex, especially quercetin seems more stable than catechin. Specifically, the results reported here support a mechanism by which VAL 443 reside, which shows the stable RMSD and RMSF profile. Both ligand shows the stable RMSD and RMSF profile in MD study.

Abbreviations

ADME	Absorption, Distribution, metabolism, Extraction
DPP-IV	Dipeptidyl peptidase-IV
GLP	Glucagon-like peptide
RMSF	Root mean squared fluctuations
RMSD	Root mean squared deviation

Declarations

Conflicts of interest/Competing interests:

The authors declare no competing interest.

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NA

Author Contribution

Authors' contributions: Conceptualization: Amita Verma; Data collection: Brijraj Singh, Ankit Kumar Singh, Writing the manuscript: Brijraj Singh, Ankit Kumar singh; Sketching of figures and data interpretation: Adarsh Kumar, Jagat Pal Yadav; Writing, review and final editing of the manuscript: Jorge L. Mejía-Méndez, Pradeep Kumar and Amita Verma.

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Code availability:

NA

Data Availability:

The data that support the findings of this study are openly available

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Tables

Table 1 is available in the Supplementary Files section.

Figures

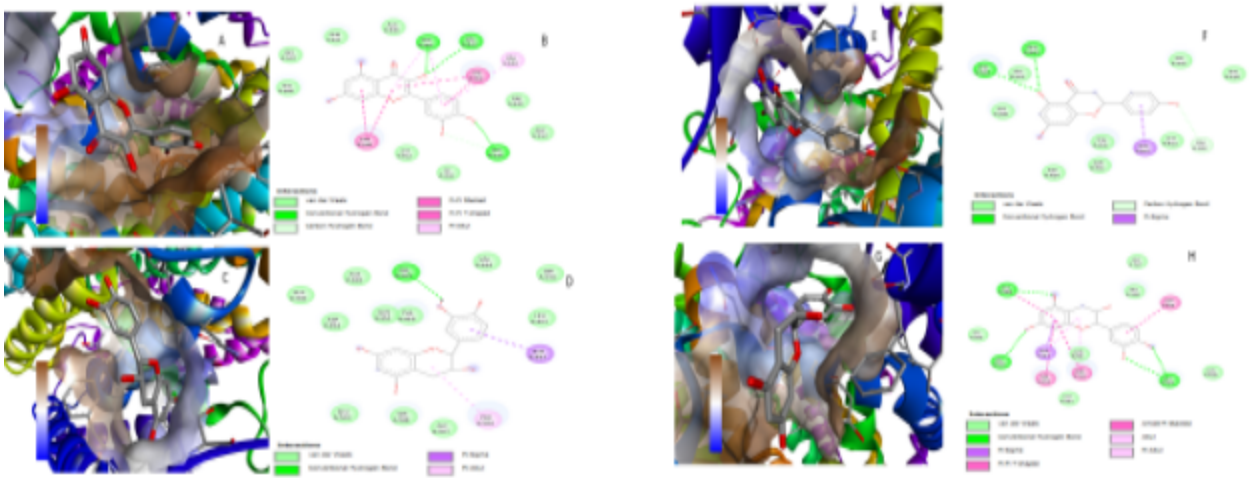


Figure 1

The protein-ligand interactions of the binding pose of the DPP4 inhibitor. **(A and B)** shows the 3D interaction and 2D interaction of the quercetin. **(C and D)** shows about catechin. **(E and F)** shows naringenin. **(G and H)** Epicatechin complex.

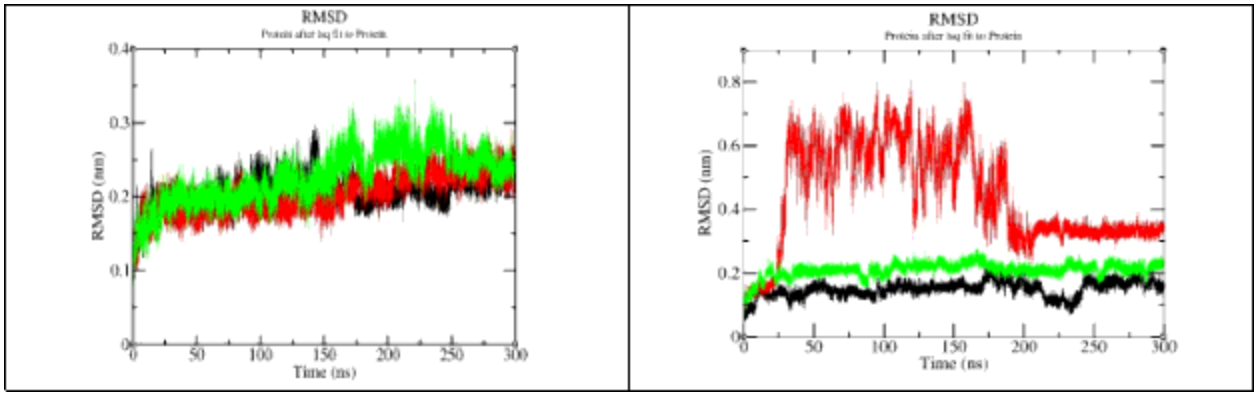


Figure 2

Root mean square deviation of quercetin (left) and catechin (right) up to 300 ns. Quercetin shows stable RMSD plot of 0.1 nm to 0.3 nm for all three replica. Catechin two replica shows the stable RMSD plot of 0.1 nm to 0.3 nm while one replica shows high deviation from 25 ns to 200 ns with fluctuation up to 0.2 nm to 0.8 nm.

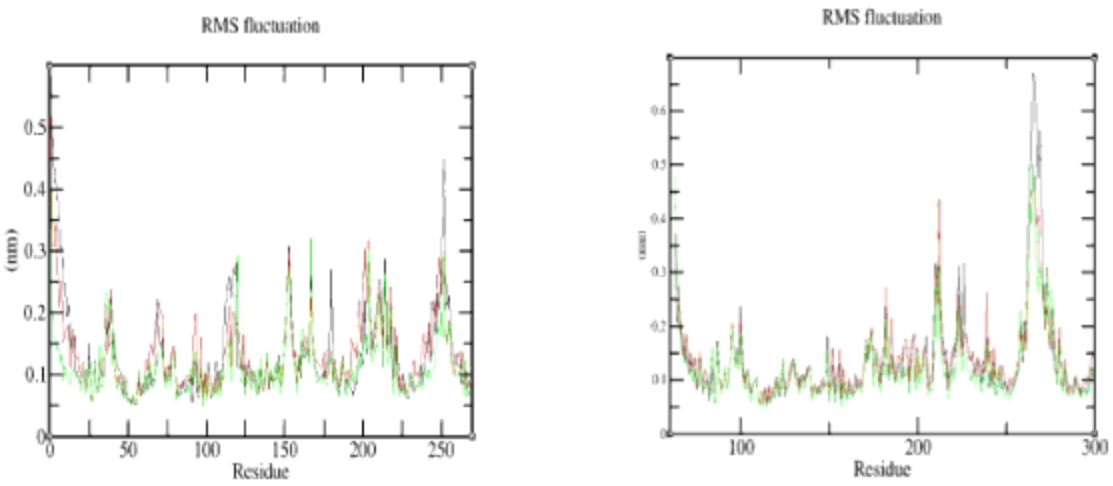


Figure 3

Root mean square fluctuations of the quercetin (left) and catechin (right) complex with DPP4 protein. It illustrate only unstable residues with complex and all three replicas shows similar fluctuation pattern for both ligand.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Table1.docx